ADVANCES IN THE MANAGEMENT OF LYMPHOMAS

*Transcription of a Panel Meeting on Therapeutics**

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* Presented at the Monthly Panel Meeting (Seventh Series), at The New York Academy of Medicine.

MODERATOR FORKNER: Before starting the panel discussion, I shall delineate the subject a bit. May I have the first slide—

(Slide) This is a classification which depicts the relationship between the diseases we are to discuss. At the top are the leukemic disorders, including so-called plasma cell leukemia, myelocytic leukemia, lymphocytic leukemia, lymphoblastic lymphosarcoma, giant follicular lymphosarcoma, reticulum cell lymphosarcoma, and Hodgkin's disease of three varieties. You will see that these diseases somewhat overlap. Lymphoblastoma, or malignant lymphoma, is a general term which includes lymphocytic leukemia, leukosarcoma, the varieties of lymphosarcoma, and the three varieties of Hodgkin's disease. Lymphocytic leukemia and lymphocytic lymphosarcoma are perhaps the same disease. If one follows the patients having chronic lymphocytic leukemia for a long enough period, at least 50 per cent of them will eventually exhibit a leukemic blood picture. We do not know the cause of any of these diseases. They are all disorders which are invasive, behaving like tumors. As lymphoblastoma involves the lymph nodes it tends to destroy their normal architecture. Some of the lymphoblastomas tend to invade the blood stream whereas others do not.

Hodgkin's disease has certain other characteristics, the presence of so-called Dorothy Reed or Sternberg cells, the presence often of eosinophils and of fibrous tissue.

The first effective treatment for this group of diseases was irradiation therapy with x-rays, employed by Pusey in 1902. He thought that he had cured some of these diseases because of remarkable effects, using relatively low doses of irradiation.

Although these disorders behave like malignant disease they are not always rapidly fatal. For example, a patient who died last week at The New York Hospital was first observed to have Hodgkin's disease in 1934. Repeated biopsies confirmed the diagnosis. Yet after 25 years of Hodgkin's disease, she died of chickenpox. At death she had extensive Hodgkin's disease and was markedly debilitated.

Another patient had lymphosarcoma diagnosed by biopsy in 1944. From 1944 to 1952 she was treated with x-rays, but then, for four years, she received no treatment for the lymphosarcoma and, on clinical examination, no evidence of lymphosarcoma was found. She died of another disease 14 years after the original diagnosis. At autopsy only three small nodules of lymphosarcoma were found, one in the

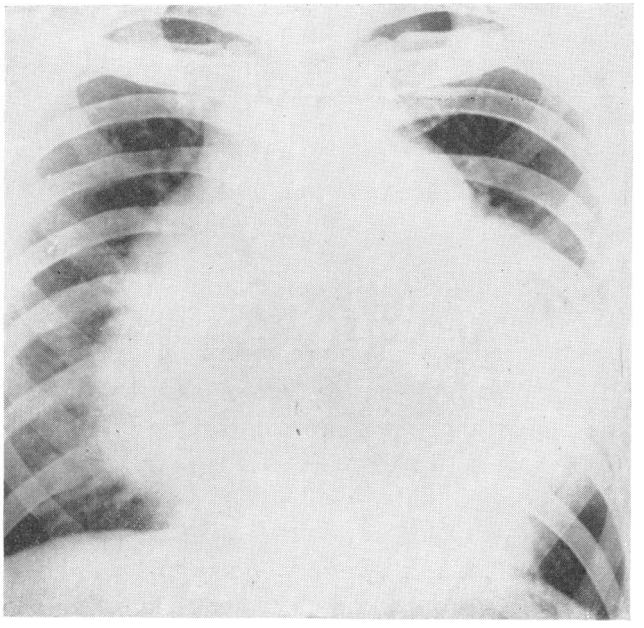

Fig. 1. Mediastinal lymphoma in 1935, before treatment. Patient is free of disease today, 24 years later.

right kidney, and two in the left kidney. The lymph nodes and other tissues were free of the disease.

I mention these cases because it is important to know that people may live for many years after the lymphoblastoma becomes evident. Each of these two patients died of other causes, after having lived many years with the disease.

Dr. Friedman will now discuss therapy with various forms of irradiation.

DR. MILTON FRIEDMAN: Twenty-four years ago a dentist, aged 33 years, came to me for treatment of a large mediastinal tumor (Figure 1). A 200 kv. x-ray machine was used to deliver a tumor dose of 1385 roentgens in 40 days. The mass in his mediastinum disappeared, and he is well today. He is a grandfather. This case illustrates one concept pertaining to most lymphomas. A patient developing a malignant lymphoma is destined to live a certain reduced span of years. This span will be shortened further if the toxic component of the disease debilitates him, or if one of the lesions involves a critical organ such as the spinal cord or the brain. Treatment averts a precipitous death or neutra-

TABLE I—CLINICAL STAGE ON ADMISSION

Stage	*No. of cases*	*Percentage*
I	48	22
II	32	15
III	136	63
Totals	216	100

lizes each recrudescence of the disease with its accompanying toxic factor. If our treatment is efficiently designed to retard the disease, the patient will live for the maximum allotted time, and this can be 25 years or longer.

This case that I have just presented illustrates the fact that the patient was destined to live a long period of time; I do not ascribe his 24 years of survival exclusively to the x-ray treatment.

I would like to tell about an interesting group of 216 cases of Hodgkin's disease, treated during World War II at Walter Reed Army Hospital. It is significant because it is a large number of cases treated in one institution over a period of five years by one individual, and with a consistent policy of irradiation. The lesions were divided into three stages:

CLINICAL CLASSIFICATIONS OF HODGKIN'S DISEASE

Stage I. Limited to a single lymph node group or to a single lesion in any organ, without constitutional symptoms.
Stage II. Disease limited to two adjacent lymph node groups, or to a single organ lesion plus regional lymph node involvement, with or without constitutional symptoms.
Stage III. Involvement of two separate lymph node groups or of multiple groups of lymph nodes, and/or more than one organ involved, with constitutional symptoms.

Note that in Table I almost two-thirds of the patients in this series were in Stage III when first seen. Our overall five-year survival rate—that is survival, with or without disease, from the onset of disease—was 44 per cent.

When based on the date of the first treatment, the five-year survival rate was 37 per cent, one of the highest survival rates reported.

TABLE II—SURVIVAL RATES BASED ON DATE OF ONSET OF DISEASE

Stage	*No. of cases*	*5 year survivals*	*10 year survivals*
I	48 (22%)	29 (60%)	9 (18%)
II	32 (15%)	15 (46%)	7 (21%)
III	136 (63%)	53 (38%)	8 (5%)
Totals	216 (100%)	97 (44%)	24 (11%)

Lost to follow-up and considered dead: Two cases.
Survivors may or may not have active disease.
Longest survivor is living and well 18 years after onset of disease.

TABLE III—SURVIVAL RATES BASED ON DATE OF FIRST X-RAY TREATMENT

Stage	*No. of cases*	*5 year survivors*	*10 year survivors*
I	48 (22%)	24 (50%)	6 (12%)
II	32 (15%)	14 (43%)	3 (9%)
III	136 (63%)	44 (32%)	6 (4%)
Totals	216 (100%)	82 (37%)	15 (6%)

In a series reported from Toronto by Dr. Peters, using similar treatment technique, the five-year survival rate was similar to mine, 38 per cent. The principle of treatment used in both instances was the same, i.e., predominant use of aggressive irradiation.

A few of the Stage III patients who survived more than five years are illustrated in Figures 2 and 3. One patient had infiltration of the lung itself in addition to widespread lymphadenopathy. Some of the patients had constitutional symptoms and bone involvement, and still survived five years. One of the reasons for the high survival rates was that the irradiation was aggressive and extensive. The dose differed from patient to patient according to the radiosensitivity of the tumor. We also irradiated prophylactically the uninvolved cervical, axillary and inguinal lymph nodes, even though it entailed two or three months' treatment with 40 to 90 doses.

The technique of treatment, especially the dose of x-rays, is very important. There is no standard dose of x-rays, because some Hodgkin's disease nodes can be destroyed with 800 r and others may require 3500 r.

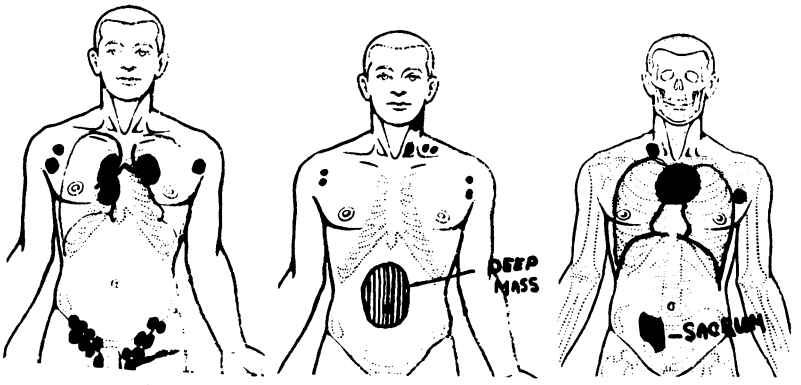

Fig. 2. Examples of Stage III patients who survived *more than five years* following treatment with aggressive irradiation. The patient in the center originally had severe backache caused by the retroperitoneal mass. The patient on the right had a destructive lesion of the right side of the sacrum.

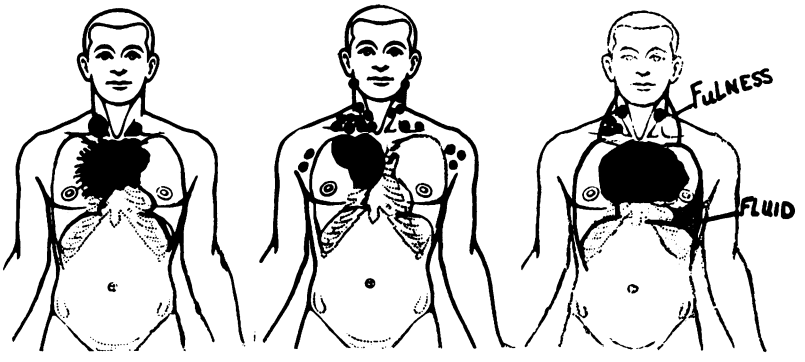

Fig. 3. Examples of Stage III patients who survived *more than five years* following aggressive irradiation. In the patient on the left the disease diffusely invaded the lung.

If the tumor is very radiosensitive, then the six peripheral node areas (cervical, axillary and inguinal) can be irradiated in 18 treatments. If it is resistant, 60 treatments may be required. Thus it is important to ascertain the correct dose for each patient.

We therefore irradiate the first group of nodes with a standard tumor dose of 1200 r in one week. If the tumor is very radiosensitive, it will disappear completely during the first week of treatment. For additional surety, we then bring the total tumor dose up to 1800 r in 10 or 12 days. On the other hand, if the tumor has shrunken only 10 per cent or 15 per cent when examined on the tenth day after the first treatment, it will require the maximum dose (3500 r) for its eradication; and the supplementary irradiation is given over a period of two

to three weeks. Usually, all the nodes in the same patient require similar dosage, except in the terminal few months of the disease when the lesion becomes more resistant. With our technique the irradiated nodes do not recur in 90 per cent of the patients. In the remaining 10 per cent of the cases, the irradiated nodes recur, usually in the terminal phase when the disease becomes fulminating and widespread. When the initial doses are small, recurrence may take place and the new nodes become progressively more radioresistant.

Little or no chemotherapy was given to this series of patients. Dr. Karnofsky was in the Army when he pioneered in the use of nitrogen mustard for lymphoma. He provided us with nitrogen mustard for the treatment of some of the earlier cases. However, very few of our patients received nitrogen mustard. When a patient had one group of nodes, as in the right neck, we irradiated the right and left neck and both axillary and inguinal nodes. It has been questioned whether this prophylactic irradiation is necessary. Our results, as well as those of Dr. Peters, tend to support the procedure used.

The modern supervoltage x-ray machines now enable us to deliver easily the proper dose to the deep nodes in the chest and abdomen when they are involved in the disease process.

To summarize: Improved survival rates are due to three features: aggressive irradiation with the proper dose for each tumor; prophylactic irradiation of the involved nodes; and supervoltage x-rays. In my opinion, nitrogen mustard, with few exceptions, should not be used in the early phase of treatment, even with widespread disease and constitutional symptoms. It should be reserved for the terminal phase of the disease when various chemotherapeutic agents are used.

MODERATOR FORKNER: *Is the supervoltage treatment comparable to the use of a cobalt unit?*

DR. FRIEDMAN: Yes. Cobalt machines give supervoltage x-rays; however, there are very few cobalt machines that are properly designed and constructed. Most of them are compromise apparatuses.

Table IV gives a summary of several reports in the world literature. It illustrates the progressive increase in survival rates when modern irradiation techniques are used.

A current question is, "When should nitrogen mustard be employed?" Our evidence, and that of Peters, relegates the drug to a secondary role, to be used in the terminal phase of the disease or in rare

TABLE IV—HODGKIN'S DISEASE
COMPARATIVE SURVIVAL RATES

Author	*Place*	*Date of Report*	*No. of Cases in Survey*	*Percentage 5 yr. Surv.*	*Percentage 10 yr. Surv.*
Krumbhaar	University of Penn.	1939	—	15%	6%
Slaughter & Craver	Memorial Hospital	1942	265	17.7	3.4
Merner & Stenstrom	Minneapolis	1947	185	21	8
Healy, Amory and Friedman	Walter Reed Army Hosp. Washington	1953	216	37	6
Paterson and Paterson	Christie Hosp.	1954	256	25	—
Levinson et al.	Univ. of Utah	1957	58	31	0
Craver, Diamond and Spitz	Memorial Hospital	1957	713	19.5	7.2
Peters	Toronto Gen. Hospital	1958	291	38	24

situations. Levinson, Wintrobe and associates (1957) find no demonstrable difference between treatment with x-rays or mechlorethamine hydrochloride; however, their published evidence does not strongly support this deduction, especially since they used the drug exclusively in only a few cases and used mostly irradiation.

There is an unfortunate tendency on the part of general practitioners and internists to use conservative chemotherapy early in the course of Hodgkin's disease. This should be discouraged, as the results to date are not as good as with aggressive irradiation.

MODERATOR FORKNER: I have asked Dr. Gellhorn and Dr. Karnofsky to discuss the chemotherapy of this group of diseases.

DR. DAVID A. KARNOFSKY: The emphasis in my discussion this afternoon will be more on the management of the special manifestations and on the different types of lymphomas. Dr. Gellhorn seemed to be in a pessimistic mood when I talked with him earlier. He decided to discuss the toxic effects of chemotherapeutic agents, and I will discuss their therapeutic value.

In the management of lymphomas the most important group of drugs available are the polyfunctional alkylating agents, of which nitrogen mustard is a representative. A point of major importance, before discussing the use of these agents, is to decide how we feel about the variety of polyfunctional alkylating agents available for clinical use.

FIG. 4—VARIATIONS IN PROPERTIES OF HN2 ANALOGUES

CHEMICAL STRUCTURE
CHEMICAL PROPERTIES —
Solubility,
Stability
CHEMICAL REACTIVITY
Various pH's,
Various substrates
NEUROLOGIC EFFECTS —
Convulsive,
Cholinergic,
Psychogenic

FIG. 5—SIMILARITIES IN ACTIVE HN2 ANALOGUES

Alkylating compounds
Two or more functional groups
Mutagenic and carcinogenic activity (when tested)
Bone marrow depression
Tumor growth inhibition
Effects on mammalian tumors in chick embryo

We have to decide whether these agents have important quantitative or qualitative differences in activity or whether they represent a group of drugs with a common mechanism of action.

We have reviewed the properties of these agents, and Figure 4 shows clearly that these derivatives differ greatly in their chemical and acute pharmacological properties. The chemical structures are different. Their chemical properties are different; for example, in their stability in solution, optimal pH at which they react, selective reactivity with different substrates, and acute pharmacological effects, such as convulsive properties, cholinergic effects and production of psychogenic disturbances. There is no question that these various agents have many pharmacological and chemical differences. On the other hand, these compounds have similar activities as concerns their effects on proliferating tissues (Figure 5).

Wherever these effective polyfunctional agents have been studied systematically, certain common activities are found. For optimal effec-

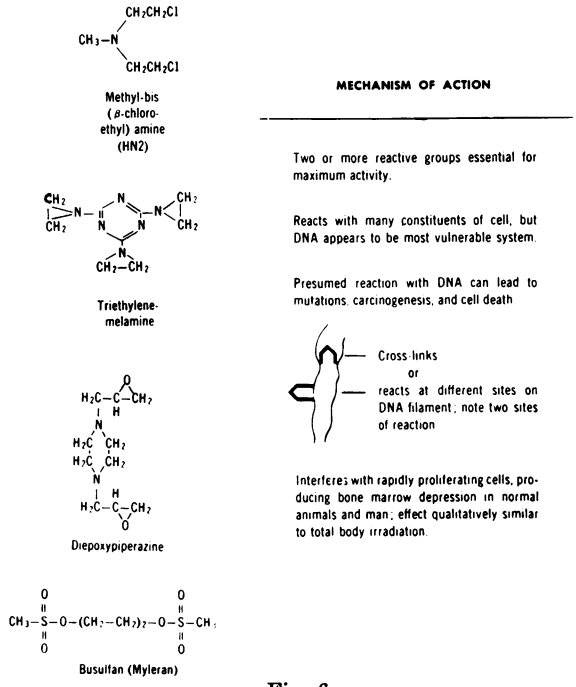

Fig. 6.

tiveness they require two or more functional or reactive groups. They are mutagenic in bacteria and Drosophila, and carcinogenic in laboratory animals. In adequate dosage they all produce severe bone marrow depression, intestinal injury and delayed deaths in experimental animals. They inhibit the growth of transplantable tumors in rodents, and, in a special system, they are capable of selectively destroying mammalian tumors growing in the chorio-allantoic membrane of the chick embryo at doses not lethal to the embryo. Thus they have a great deal in common in their biological effects.

There are many different types of alkylating agents available (Figure 6). We have sulfur mustard, which Dr. Louis Alpert has recently studied. He finds that the effects it produces are similar to those produced by nitrogen mustard. We have nitrogen mustard, and a number of related compounds, such as chlorambucil (Leukeran), sarcolysin (Melphalan, PAM) and Endoxan or Cytoxan, ethylamine derivatives such as TEM, Thio-TEPA and E-39, an entirely different type of substance, sulfonyl methane esters such as busulfan (Myleran), which chemically is an alkylating agent. Recently there have been studies with diepoxy-

piperazine, another different chemical which has effects similar to nitrogen mustard. In Germany, another type of nitrogen mustard, Endoxan, has been described, which is said to be less toxic as far as bone marrow depression is concerned, and to have increased evidence of therapeutic activity. From our own experience and from a review of the evidence, I don't believe we can support the view that there is any important difference in the therapeutic effects of these various alkylating agents. They all have the same spectrum of biological activity and they produce therapeutic effects with approximately the same degree of toxicity as far as the patient is concerned. It is conceivable that some day someone may find a nitrogen mustard which will affect lymphomas without producing bone marrow depression. Thus far, however, there is no convincing evidence that we are approaching this situation.

On the other hand, different mustards have various conveniences in use. For example, nitrogen mustard or HN2 is given by intravenous injection, and one can give a rapid course of treatment. TEM can be given intravenously and orally and does not cause nausea and vomiting to the same extent.

Chlorambucil can be given orally by daily administration and one can, in suitable cases, obtain smooth and prolonged control in patients with systemic manifestations of lymphoma. In our opinion, nitrogen mustard and chlorambucil are adequate representatives of the alkylating agents for clinical use.

What are the indications for the use of the polyfunctional alkylating agents in Hodgkin's disease or lymphomas? I would like to cite four situations in which I think they have been useful. The first situation is in early management of Hodgkin's disease. I certainly agree with Dr. Friedman that localized radiotherapy is by far the most effective method of managing this disease. However, in early cases where the disease appeared to be confined to one major area, such as mediastinal and cervical nodes, we have been interested in combining a course of nitrogen mustard intravenously with intensive local radiotherapy. The reasons for this are: first, that there may be some additive local effect from the two forms of treatment; and secondly, if some lymphoma cells are scattered to other areas, perhaps the nitrogen mustard may have some effect in either destroying these cells, or at least delaying the recurrence of the disease. This is an uncertain indication for nitrogen mustard. The combined procedure, however, has done no harm, and possibly it may

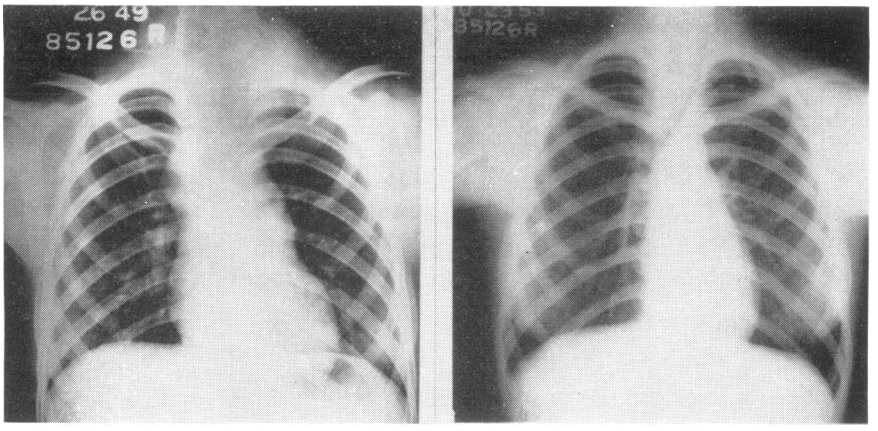

Fig. 7.

produce an increased number of long survivors. This is a matter of many years of study.

An example of this combination is shown in Figure 7. An 11 year old girl received, in 1949, a course of nitrogen mustard, followed by intensive x-ray therapy for Hodgkin's disease involving the mediastinum and cervical nodes. There has been no evidence of recurrence to the present. This illustrates a response to the procedure, but an isolated result does not, of course, prove the additional value of nitrogen mustard.

The second and major indication for these agents is the symptomatic patients with Hodgkin's disease who have fever, itching, anorexia or weakness. In these patients excellent symptomatic relief may be obtained for long periods of time by the administration of suitable doses of nitrogen mustard or related compounds. Again, local radiotherapy, if the exact location of the disease is known, is preferable, but if it is hard to localize the disease, then a systemic medication is useful.

Figure 8 shows a patient who had extensive radiotherapy to the mediastinum for a number of years, but returned with cough and fever. Further x-ray treatment to the chest was considered to be hazardous because of the possibility of inducing pulmonary fibrosis. For a period of eight months this patient was maintained on oral TEM, and initially she showed an excellent response. However, she finally became resistant and died of disseminated disease.

The third indication is a situation in which local disease is threatening life, and a prompt therapeutic response is essential. Examples of these problems are: spinal cord compression with rapidly developing

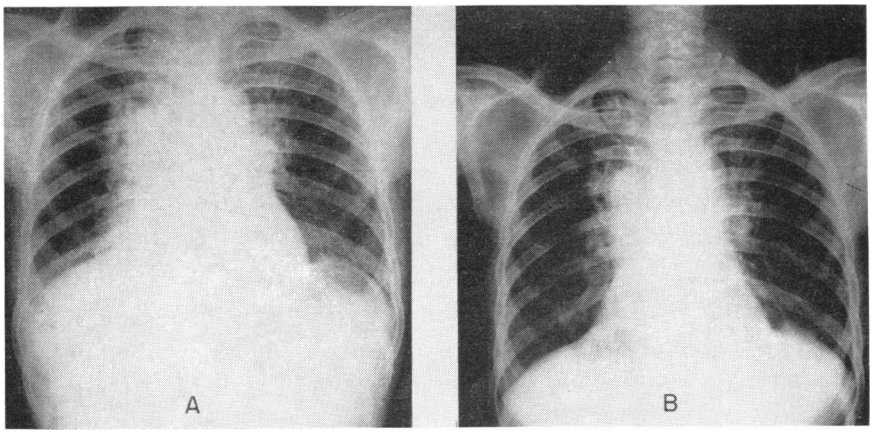

Fig. 8.

evidence of paralysis; cardiac tamponade due to pericardial involvement; or compression of the trachea. In these situations we have given nitrogen mustard, 0.4 mg./kg. in single doses with prompt relief, in many cases, of symptoms and signs produced by the local disease. This treatment is followed immediately by intensive radiotherapy to the involved area in order to prolong the response. Thus we have a combination of immediate relief produced with less hazard than from the use of local radiotherapy, because x-rays may take several days to produce a response, and they are reputed at times to cause swelling of the tumor before it begins to regress, with a prolonged local effect resulting from local radiotherapy.

A fourth indication is in patients who have advanced Hodgkin's disease, who have had a maximum amount of x-ray therapy, and who seem refractory to any further treatment. In these situations we believe it essential that the patient receive an adequate trial of some type of alkylating compound. Occasionally one can obtain a very satisfactory and prolonged response, and in such cases, the patient can be continued on further maintenance courses of HN2 or chlorambucil or a further trial of local radiotherapy.

Finally, we have used nitrogen mustard occasionally as a diagnostic test. One patient I can cite will illustrate this point. This was a 17 year old boy who developed pleural effusion with parenchymal infiltration, a large liver and a temperature of 106° F. This boy had several lymph node biopsies which were inconclusive. He was treated with many different antibiotics without effect on his persistent fever. The pleural

effusion was aspirated for diagnostic purposes and was classified as Class IV Papanicolaou, strongly suggestive of lymphosarcoma. This boy was put on adrenal steroids without improvement. He was given streptomycin and isoniazid because of the possibility of tuberculosis, without any benefit. His deterioration was marked, and death appeared to be a definite probability within a few days. He was given, therefore, a therapeutic trial of TEM. Within 48 hours the fever began to decrease and all manifestations of disease cleared. This was more than three years ago, and he has shown no recurrence to date. We don't know the exact nature of this boy's illness. Rather than be inactive when things were going badly, and when trials of antibiotics and steroids failed, it was advisable to give him a trial of the polyfunctional alkylating agents.

In closing, I would say that these agents have an important role in the management of lymphomas, but I will certainly not argue with Dr. Friedman about the superiority of radiotherapy in the great majority of situations.

MODERATOR FORKNER: *Dr. Karnofsky, what are the disadvantages of using alkylating agents?*

DR. KARNOFSKY: If I answer that Dr. Gellhorn will have nothing to say!

MODERATOR FORKNER: We shall skip Dr. Gellhorn for the moment and call on Dr. Burchenal.

DR. JOSEPH H. BURCHENAL: Dr. Forkner has asked me to talk about the uses of the steroids in lymphomas. Generally speaking, I think that the steroids should be saved until after the radiation therapy and nitrogen mustard-type agents have had their chance. It is true that the steroids will have a definite effect in decreasing the size of the liver, of the spleen and of the tumor masses in lymphosarcoma, reticulum cell sarcoma, and in chronic lymphocytic leukemia. However, they do not do it any better than radiation or nitrogen mustard, and generally not as well. For some strange reason in chronic lymphocytic leukemia, as nodes shrink and liver and spleen become smaller under steroid therapy, the white count very often increases. It is almost as if one squeezed the nodes and forced the cells out into the peripheral blood. Eventually, after longer therapy with steroids, the white counts will often return to reasonable levels and sometimes to a normal level. It seems to me that the greatest use of steroids in the lymphomas is in combating the hemolytic component of the disease. This is particularly true in chronic

lymphocytic leukemia, perhaps somewhat less so in lymphosarcoma, reticulum cell sarcoma and in Hodgkin's disease. Thrombopenia also occasionally occurs in these diseases, unconnected with therapy. It can also be a toxic manifestation, particularly of mustard therapy, as Dr. Gellhorn will discuss. For the thrombopenia that is on an immunological basis, the steroids are quite useful. This is particularly important, because this is the type of situation that cannot be treated well by mustard therapy, although radiation will sometimes handle it.

I don't believe that the steroids play much of a role in Hodgkin's disease, as far as active therapy of the disease itself is concerned. They can be used as supportive therapy in the patient who is very sick with a high fever and almost terminal. They can be used to hold the line between courses of radiotherapy or mustard therapy, but they do not have much effect *per se* in the treatment of the disease, although they are useful whenever a hemolytic or thrombocytopenic state is present.

As to the compounds that can be used, one can use ACTH to stimulate the patient's own adrenals, either by intramuscular administration in the form of gel, or intravenously by constant intravenous drip. Ordinarily, however, ACTH therapy will not be necessary, and one can use oral medication, such as cortisone, prednisone, or decamethazone. In general, I think one would now use a prednisone type of agent, as it does not have the undesirable effect on electrolytes that one sees with cortisone. One can use prednisone, Medrol, triamcinolone or decamethazone. At the present time I don't believe that we have any indication that one is any better than another, but I do think that this general group is superior to cortisone, because of the lack of effect on electrolytes.

When one is trying to treat chronic lymphocytic leukemia, lymphosarcoma or reticulum cell sarcoma, and to decrease the size of a massive liver and spleen, then I think one needs to use what we consider standard doses, which would be something between 100 and 200 mg. a day of prednisone, obviously divided into q.6.h. dosage. Although I don't believe that it is often necessary, one can also use massive doses of prednisone up to a gram a day, but I see relatively little indication for that. In order to combat the hemolysis or the thrombopenic states, smaller doses oftentimes are quite adequate, and we have seen patients who have been handled quite well on 20 to 40 mg. of prednisone per day. Dr. Forkner mentioned one case he had seen that had continued for a

very long period of time. I might mention a case that had been referred to me by Dr. Weisberger, in which death may possibly be attributed to the patient's having stopped taking his steroids. This man was president of a company, a very active man. At 72 years of age, he came to New York on a little holiday and stopped taking the steroids on which he had been maintained for some time because of difficulty with purpura. When he stopped the steroids, the purpura became much worse and he seems to have died of a cerebrovascular accident, in the 38th year of the disease. He was a fully useful member of society until a day or two before his death, a case that shows that chronic lymphocytic leukemia occasionally can be a very long drawn out disease and one that does not necessarily reduce the normal life span. This patient's long course was probably attributable to the nature of his disease, to the fact that he was aggressively treated with radiotherapy whenever necessary, and only in the latter stage of the disease with steroids. Dr. Gellhorn will discuss the various undesirable side effects of these steroids.

To sum up, I feel that the steroids should be saved for the very special situations, primarily the hemolytic and thrombopenic aspects of these diseases, and should be used only after radiation therapy and mustard therapy have been given their chance.

MODERATOR FORKNER: Dr. Gellhorn!

DR. ALFRED GELLHORN: We have heard about the management of this group of patients, and all of us in this room have had and will continue to have the opportunity and responsibility of treating these diseases. This is difficult, as we all know, because of their chronicity and the multiple problems which arise. We have heard indications for drug use, we have heard results that can be anticipated, and now it is only necessary to review together some of the things which we must keep in mind in the proper use of these agents; namely, the side effects that can come from the agents alone and that can come from the agents in conjunction with the natural history of the disease.

Let us start, because it was started thus on the panel, with a discussion of some of the side effects to be kept in mind when we refer our patient for radiotherapy. When the disease is localized and aggressive therapy is given, there are usually no significant complications that we, as referring physicians, will contend with, except that the patients may call us and tell us that the x-ray man has given them a terrible burn. Those of us who are not in radiology have a real responsibility to make

clear to the patient this statement about radiation burns, because it is loosely used by patients. Either by concurring, because it is the easy way, or not making comment, physicians frequently seem to give tacit agreement. We should explain that the skin erythema is an expected reaction and will subside. When localized disease is present in the supraclavicular areas, and heavy radiation is to be given to this area, it is important to know that there is not an underlying acid-fast lesion present. Irradiation in this situation can lead to miliary dissemination of tuberculosis. An appropriate anti-tuberculosis prophylactic chemotherapeutic regimen should be instituted before initiating radiotherapy. When Dr. Friedman indicates he has tried aggressive radiotherapy to multiple sites, then we may encounter some other complications. Thus, if radiotherapy is used in multiple areas, there may well be a depression of bone marrow similar to that observed with alkylating agents, with all the attendant problems that arise from such an effect. In addition, if irradiation is given to mediastinal structures, and possibly repeatedly, problems of fibrous tissue reaction in the irradiated tissue may occur and the patient may ultimately have impaired respiration due to pulmonary fibrosis.

Turning now to chemotherapeutic agents, the list of side reactions and complications is considerable. On the other hand, if we recognize them and know the mechanisms that are behind them, these agents, as has been indicated by Drs. Karnofsky and Burchenal, are tremendously valuable in our management of patients with lymphomas.

(Slide) In the case of the alkylating agents, as Dr. Karnofsky has indicated, the drug most frequently used, even nowadays, is nitrogen mustard given intravenously. This has two major effects. One is on the central nervous system, an immediate toxic effect, and it is manifested by stimulation of the vomiting center, producing the nausea and vomiting with which we are all familiar. At the present time, with the drugs available for combating such a reaction from the stimulation of the vomiting center, this type of side effect can be markedly minimized. The other important effect of nitrogen mustard is on bone marrow functions. As you know, the effect is not immediately apparent, but there is a delay, and usually the peak effect, as manifested by changes in peripheral blood, can be seen within 7 to 15 days following the completion of a standard course of nitrogen mustard given intravenously. There are several things which I think are worth re-emphasizing. Al-

though there is a pancytopenia in many instances, the leukopenia is characterized not by agranulocytosis, but by lymphocytopenia. Although the total count may be reduced, the proportion of neutrophils present remains high and therefore the frequency of infections is not as high as one would anticipate. Severe thrombocytopenia does not usually occur the first time that the patient is given a chemotherapeutic agent; but in patients who have had previous treatment, thrombocytopenic bleeding may be an important complication. Dr. Burchenal has indicated one of the means of attempting to modify this particular reaction.

The anemia that does occur is one that is usually self-correctable if a remission is produced in the disease.

With regard to other alkylating agents, triethylene melamine (TEM), TEPA, chlorambucil, uracil mustard, which is really just another nitrogen mustard, the side effects are qualitatively similar to those of nitrogen mustard. Usually, the stimulation of the vomiting center is less with the majority of these and therefore nausea and vomiting are not prominent symptoms. Marrow depression also occurs, but because these other agents have a variable rate of absorption from the gastrointestinal tract when given by mouth, or have a more delayed onset of effect when given parenterally as in the case of Thio-TEPA, they are less predictable, in terms of marrow depression, than nitrogen mustard. This is important for us to bear in mind if we plan to use these agents, for we should not necessarily anticipate that our peak depression in blood count will appear at the end of two weeks. Rather, we should keep observing patients over a period of three weeks, or even more, before going on with higher doses than those recommended.

(Slide) There are, in addition, certain complications that occur with alkylating agents that it would be well to mention, particularly in patients with lymphomas. These have to do with infection, not necessarily because of leukopenia, but when the leukopenia is combined with a depression of the normal gamma globulin, a phenomenon which occurs in approximately 30 per cent of the patients with lymphosarcoma and chronic lymphatic leukemia. It has been observed in a group of patients studied at our institution that, with hypogammaglobulinemia, infections not only occur with greater frequency in these patients than in those with lymphoma and no hypogammaglobulinemia, but the morbidity is considerably greater.

Also, since these agents may have a dramatic effect on a tumor when given, there may be a rapid dissolution of tumor and the blood uric acid may become markedly elevated, leading to renal complications. One must therefore bear in mind that hyperuricemia is possible, know about it beforehand and take appropriate measures, such as adequate hydration, to prevent its leading to significant damage of renal function.

On rare occasions, following the administration of nitrogen mustard, dissemination of miliary acid-fast infection may occur. It is well to keep this in mind. Know your patient in order to be forewarned and prevent such a possibility.

Turning to the steroids which Dr. Burchenal has presented, we shall review the side effects known to all of us. These include the Cushing facies, the important problem of gastrointestinal ulceration and therefore the necessity, when our patients are put on dosages such as Dr. Burchenal suggests of 100 mg. of prednisone, of placing the patient on a well-planned and specific ulcer regimen. The psychic effects of these steroids are important. We hope that the patients will have a euphoric reaction, but many of them become paranoid, and this effect must be looked for in our contacts with the patient in order to prevent disastrous results. Electrolyte changes can occur with these agents. Again, even though the compounds mentioned by Dr. Burchenal cause less sodium retention than cortisone, nevertheless, in the doses that we employ, there may be sodium retention with the associated edema; there may also be loss of potassium and attendant manifestations of asthenia from hypokalemia. Therefore, when patients are put on large doses, additional potassium chloride is given. Patients should be examined before being put on steroids, to determine whether they have any evidence of diabetes, for there will certainly be increased hyperglycemia, glycosuria, and the hazard of diabetic acidosis.

It is also well to bear in mind that patients on any of these doses of steroids over prolonged periods of time have a greater susceptibility and frequency of infection with saprophytic organisms such as with monilia. This not only presents local problems in the buccal cavity, but can produce systemic infection. The fungi are important, in terms of their systemic infection of the lungs or, perhaps even more important, involvement of the central nervous system, as by cryptococci. Other infections also have an opportunity for dissemination, pyogenic and tuberculous being the ones that should be borne in mind.

Finally, we must be aware that, if our patients are to be placed on these agents for control of hemolytic activity for a considerable period of time, there will be a depression of osteoid deposits. The x-ray will demonstrate progressive osteoporosis; and it can be anticipated that a significant number of our patients will develop compression fractures with the symptoms attendant thereon. These, then, are some of the side reactions. It seems to me that none of them constitutes such overwhelming contraindications that we would not consider the use of either irradiation or the chemotherapeutic agents, but certainly we must know them in order to manage our patient well and totally.

MODERATOR FORKNER: I gather, Dr. Gellhorn, that you are not quite in agreement with Dr. Friedman about aggressive treatment. My feeling has always been that, with this group of incurable patients, all one can hope to do is to improve them symptomatically and to prolong their useful lives. In my experience, the minimum amount of x-ray therapy which can relieve the symptoms is the desirable amount, rather than the administration of the maximum amount which one can deliver to any one particular area. *May we have some discussion on this subject, Dr. Friedman?*

DR. FRIEDMAN: What I mean by aggressive treatment is that dose of radiation, delivered to the diseased nodes, and to other lymph node regions prophylactically, which will prevent a recurrence of the disease in the irradiated area throughout the rest of the patient's life, with the exception of the 10 per cent of cases in whom the recurrence appears in the terminal phase of the disease. If one gives minimal doses of irradiation, they must frequently be repeated one or more times, so that the total dose delivered to each area is ultimately larger than that of a single course of the so-called aggressive irradiation that I give; and the incidence of radiation ulcers is much higher. Finally, the survival rates following the small-dose techniques are much lower than the survival rates following aggressive irradiation.

DR. GELLHORN: I would like to rise to this one. I don't believe that any person interested in chemotherapy at the present time would suggest the use of these agents in the management of disease which is clinically localized, and I believe that most of us feel that, when on clinical examination the disease is found to be limited to one site or to one region, the treatment of choice is x-ray therapy. Unlike Dr. Forkner, we believe, under these circumstances, that a tumoricidal dose should be

given. However, I think we would take real exception to Dr. Friedman's plan in an individual who has clinically evident disease in multiple sites. On the basis of what most of us observe in the natural history of the disease, the process is not limited to just those areas that we can recognize clinically but is certainly also present elsewhere. Recognizing that the human organism can tolerate only so much radiation, it seems to us unwise to deliver such tumoricidal doses to multiple sites of the body.

DR. BURCHENAL: I would like to ask Dr. Friedman a question.

DR. FRIEDMAN: May I first briefly answer Dr. Gellhorn's statement concerning the aggressive irradiation technique for widespread disease. I showed six examples of patients with widespread disease who had survived for five years, and in Table III a 32 per cent five-year survival rate for 150 patients with Stage III Hodgkin's disease. Now, Dr. Gellhorn, I think you have published some rather favorable figures. Were they comparable with mine?

DR. GELLHORN: No, no, these patients received irradiation *and* chemotherapy. When the disease was disseminated the patient received chemotherapy if the manifestations were constitutional in nature, and received irradiation for problems of pressure in various areas when this was indicated.

MODERATOR FORKNER: Dr. Burchenal!

DR. BURCHENAL: I wanted to ask Dr. Friedman if he has ever tried this. I believe it is known that in animals, if small areas of the body are irradiated, one at a time, larger doses can be given. I wonder if he has ever tried giving aggressive radiotherapy to Hodgkin's disease, taking segments of the body; for example, the lower quarter, the in-between quarters, and so on, with the idea that if one can prevent recurrence from one area one might, by covering the whole body over a given period of time, not wipe out the bone marrow, give it a chance to recover, and still prevent the Hodgkin's disease from recurring?

DR. FRIEDMAN: I have not tried it because others have tried it, with results that I anticipated; namely, with doses much lower than that required to destroy Hodgkin's disease, there was a profound depression of the bone marrow.

DR. BURCHENAL: Do you think the bone marrow in a given area would recover at all after 2000 r—if you gave a segment, say this wide (indicating), would the bone marrow in the ribs recover, if two weeks

later you were treating another segment, and later on another?

DR. FRIEDMAN: If one undertook to give 2000 r to the whole body, one would kill most of these patients. The bone marrow in each irradiated area would not recover in the period that you specify.

DR. BURCHENAL: If one took a year to do it, the patients ought to be repopulating their blood from normal bone marrow.

DR. FRIEDMAN: If one gave it over a period of a year, the marrow in many patients might recover but there would be a significant number of deaths, enough to discourage further use of the technique. I don't think radiation cures the disease. In our Walter Reed series there were about eight patients who died, and at postmortem examination there were no manifestations of the disease.

MODERATOR FORKNER: There are a number of questions from the floor. The first is referred to Dr. Karnofsky. "*A white male, age 28, for one year has had substernal discomfort, two episodes of fever unresponsive to antibiotics. X-rays of the chest show a progressively enlarging mediastinal mass and abdominal films show enlargement of the spleen, which is not clinically palpable. Routine blood counts and bone marrow aspiration biopsy were unrevealing except for slight anemia. No lymph nodes were enlarged. What is the next step? Should one explore the mediastinum for a biopsy, or should one be satisfied with watchful waiting?*" *Dr. Karnofsky, can you answer that very briefly?*

DR. KARNOFSKY: I think I can answer the question academically, although one does not always practice what one preaches. Before treating a lymphoma, except in the most remarkable circumstances, one should first make sure of the diagnosis. I realize that strenuous efforts have been made to establish a diagnosis in this case. I certainly think one should seriously consider a thoracotomy in this patient. The morbidity and mortality from that procedure are low, and it would be far more important to know whether this patient has lymphoma and treat him adequately than to forego the hazards of the thoracotomy and treat him empirically and not know what is going on until perhaps very late in the disease.

MODERATOR FORKNER: Dr. Friedman, here is a question that belongs to you. "*In view of the leukemogenic effects of radiation, are you not afraid of converting lymphoma into frank leukemia?*"

DR. FRIEDMAN: The detrimental effects of radiation have been wildly exaggerated. In general, when one is treating a patient for a specific dis-

ease, the question of leukemogenesis by radiation does not enter; the problem of leukemogenesis induced by radiation arises only when the individual being irradiated is either normal, or when one is considering extensive radiation for a very benign disease such as arthritis of the spine.

MODERATOR FORKNER: This physician asks, "*What are the comparative results of no therapy in Hodgkin's disease with radiation therapy?*"

DR. FRIEDMAN: I don't think there is a valid, comparable series of patients with Hodgkin's disease not having been irradiated. However, there is no question that in Hodgkin's disease, treated either with radiation or alkylating agents, the survival rates are much greater than without treatment. I refer you to Table IV which shows a marked increase in survival rates with modern aggressive treatment techniques.

MODERATOR FORKNER: Also, patients are made much more comfortable while they do live.

Dr. Gellhorn, will you discuss the management of the patient with intractable generalized pruritus as a result of Hodgkin's disease?

DR. GELLHORN: This is one of the very good indications for the use of nitrogen mustard, and usually an effect can be anticipated in a short period of time, with relief of distressing symptoms. The alternative is treatment of the patient with x-ray. Usually, in this instance, the treatment consists of radiation to the retroperitoneal area. This is also effective, but the onset of benefit is usually more delayed than that following intravenous administration of an alkylating agent.

MODERATOR FORKNER: *What are the effects of steroids in such cases?*

DR. GELLHORN: Steroids in such instances would also be expected to have a beneficial effect on pruritus. The reason that I would not recommend such therapy is that, once started, it is necessary to continue with the steroid, for when the steroid is discontinued the pruritus and other manifestations will promptly recur.

MODERATOR FORKNER: The next question is addressed to Dr. Friedman: "*Under what circumstances do you irradiate the liver, without irradiating the remainder of the abdomen?*"

DR. FRIEDMAN: When the liver is enlarged with disease, and the patient is not in a truly terminal phase of disease, it is a simple matter to irradiate the entire liver with large tumor doses, up to 3500 r. There is minimal or almost no radiation sickness. We use it commonly when carcinoma of the breast has metastasized predominantly to the liver. However, in lymphoma the liver becomes enlarged in the terminal phase

of the disease when one is dealing with a sick patient with anemia and general effects of the disease; under these circumstances, irradiation becomes less effective than in a healthy patient.

MODERATOR FORKNER: *Dr. Karnofsky?*

DR. KARNOFSKY: I would be a little more optimistic about liver irradiation. When the liver becomes enlarged I don't think it necessarily represents a terminal phase of the disease any more than any other generalized manifestation of the disease, and, even when alkylating compounds have not produced a satisfactory systemic response, and the liver remains enlarged, local radiotherapy of the liver has often been effective.

MODERATOR FORKNER: *Dr. Burchenal, is it true that chlorambucil is more effective against lymphocytes than against the remaining blood elements?*

DR. BURCHENAL: I think that chlorambucil, along with other nitrogen mustards, the bis beta chlorethyl compounds, do have a slightly greater effect on the lymphocytes. On the other hand, if enough is given, it will depress everything. This compound was first tested by a group at the Chester Beatty Institute. They felt that Myleran was specific for granulocytic leukemia, whereas chlorambucil was specific for lymphocytic leukemia. I don't think it is quite as black and white as that would indicate. Certainly Drs. Karnofsky, Sykes and Krakoff have shown that chlorambucil will act against chronic granulocytic leukemia and Myleran will act against some of the chronic lymphocytic leukemias.

DOCTOR: *Would radiotherapy to a massively enlarged spleen be of use in chronic myelogenous leukemia with falling hemoglobin, normal white blood cell count and normal platelets?*

MODERATOR FORKNER: The answer is yes. Any objections?

Patients with lymphoblastoma often are given large doses of vitamins by their physicians because they are ill. What do you think of that, Dr. Gellhorn?

DR. GELLHORN: I think it is fine for the vitamin manufacturers, but I don't think it does any good to the patient.

MODERATOR FORKNER: *Do you think it might do harm?*

DR. GELLHORN: Well, I suppose that if one gives enough A or enough D, one can conceivably get into problems, particularly disturbances of calcium metabolism.

MODERATOR FORKNER: *What about folic acid?*

DR. GELLHORN: I think that the rate of excretion of folic acid would probably be able to keep up with most administration, so that the vitamin does neither good nor harm.

MODERATOR FORKNER: *Dr. Burchenal, are the antifolic acid compounds of any use in this group of diseases?*

DR. BURCHENAL: In lymphosarcoma of childhood, the antifolics may occasionally work reasonably well. In lymphomas in general, they have no place. In chronic lymphocytic leukemia, or in the lymphosarcomas in adults that we have seen, they do nothing.

MODERATOR FORKNER: There is another point that I would like to bring out. If the panel disagrees with me I would like to have them say so. Patients with these diseases should not be treated simply because they have the disease. I have seen many patients in whom I have delayed treatment for months and years simply because they had no significant symptoms of the disease. They were not losing weight, had no anemia, they had no fever, no pruritus, but they did have one of these diseases. Making the diagnosis is not an indication for treatment. One should delay treatment until one gets some indication that the disease is progressive and is producing symptoms. *Is there any disagreement?*

DR. GELLHORN: I would like to make a qualification. I subscribe to that except in patients who have localized disease. In such patients, who may be asymptomatic, it is important to provide treatment for them.

DR. BURCHENAL: I would agree on not treating asymptomatic chronic lymphocycotic leukemia, but I would like to see a localized lymphoma treated aggressively immediately after the diagnosis is made, with the hope of eradicating it.

MODERATOR FORKNER: *Have you ever seen these diseases eradicated by such aggressive measures?*

DR. BURCHENAL: We have had patients with no evidence of disease for five, ten or more years. Whether or not the disease will eventually recur we cannot say.

MODERATOR FORKNER: It seems to me that if one could find a local, accessible group of nodes in Hodgkin's disease, it might be wise to extirpate the nodes with surgery and then treat with x-rays. *What is your view on that?*

DR. FRIEDMAN: There are several reports, including one by Sugarbaker, showing gratifying five-year survival rates from surgical block dissection of the regional group of nodes with Hodgkin's disease. How-

ever, most of his patients had postoperative x-ray therapy. Although block dissection and resection of a localized group of nodes is efficient, I see no reason for radical surgery, when irradiation is so much easier. Furthermore, most of the surgery patients need irradiation to other areas later on to permit them to survive five years.

DR. BURCHENAL: Would you be willing to do just surgery? Would you not want to irradiate the adjoining nodes as well?

DR. FRIEDMAN: I would prefer to use radiation initially.

DR. BURCHENAL: We would not mind using surgery if the disease were localized.

MODERATOR FORKNER: *Are there any other points the panel would like to bring out?*

DR. KARNOFSKY: That we should not do anything in the asymptomatic patient is, I think, an oversimplification. In patients with localized disease present in an area where it can produce serious complications, I think it is worth treating, rather than waiting until the patient begins to complain of symptoms.

MODERATOR FORKNER: One should watch his patients carefully in order to anticipate symptoms.

DR. KARNOFSKY: When does one start treatment? If one waits passively until the disease does something which produces symptoms, I presume you would start treating then?

MODERATOR FORKNER: The symptoms may include a loss of five or ten pounds body weight, there may be a little anemia; the patient himself may not complain, but if you watch him carefully and observe the usual features, one can almost invariably predict when these patients are going into relapse.

DR. KARNOFSKY: You are talking about doctors who spend their lives studying the disease. In general practice, apathy in management is not the same thing as the specialist predicting and anticipating and waiting until the proper stage of the disease is reached before treatment is started. I think one sometimes has to treat if a patient has no symptoms of the disease, because the disease is present in a strategic area and it may enlarge at a subsequent time to produce trouble.

MODERATOR FORKNER: In this disease, as in other diseases, one of our chief faults is overtreating the patient.

Thank you all very much.